Emergency Physician Recognition of Adverse Drug-related Events in Elder Patients Presenting to an Emergency Department

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Abstract

Objectives: The authors examined the ability of emergency physicians (EPs) to recognize adverse drug-related events (ADREs) in elder patients presenting to the emergency department (ED). **Methods:** This was a prospective observational study of patients at least 65 years of age who presented to the ED. ADREs were identified using a validated, standardized scoring system. EP recognition of ADREs was assessed through physician interview and subsequent chart review. **Results:** A total of 161 patients were enrolled in the study. Thirty-seven ADREs were identified, which occurred in 26 patients (16.2%; 95% confidence interval [CI] = 10.5% to 22.0%). The treating EPs recognized 51.2% (95% CI = 35.2% to 67.4%) of all ADREs. There was better recognition of those ADREs related to the patient's chief complaint (91%; 95% CI = 74.1% to 100%) as compared with recognition of ADREs that were not associated with the chief complaint (32.1%; 95% CI = 14.8% to 49%). EPs recognized six of seven severe ADREs (85.7%), 13 of 23 moderate ADREs (56.5%; 95% CI = 36.8% to 77%), and none of the mild ADREs. Recognition of ADREs varied with medication class. **Conclusions:** EP performance was superior at identifying severe ADREs relating to the patients' chief complaints. However, EP performance was suboptimal with respect to identifying ADREs of lower severity, having missed a significant number of ADREs of moderate severity as well as ones unrelated to the patients' chief complaints. ADRE detection methods need to be developed for the ED to aid EPs in detecting those ADREs that are most likely to be missed.
Key words: emergency department; adverse drug-related events; drug-related morbidity; physician performance. ACADEMIC EMERGENCY MEDICINE 2005; 12:197–205.

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Received January 27, 2004; revision received July 22, 2004; accepted August 10, 2004.
Presented at the Association des Médecins d'Urgence du Québec scientific meeting, Quebec City, Quebec, Canada, November 2003.
Supported by contributions from Programme MSSS - Régies régionales—FRSQ de soutien à la recherche sur la problématique des urgences, AMUQ Residency Research Bursary, the Brownstein Emergency Department Research Endowment Fund and the Armand Afilalo and Family Emergency Department Research Endowment Fund. Dr. Bérard is a research scholar from the Canadian Health Foundation and the Canadian Institutes of Health Research (Rx&D/CHIR).
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doi:10.1197/j.aem.2004.08.056

Adverse drug-related events (ADREs) are unfavorable medical events related to the use and misuse of over-the-counter and prescription medications. ADREs have emerged as important health risks, especially in elders, who tend to consume the most medications. ADREs may account for up to 28% of emergency department (ED) visits[1–3] and 30% of hospital admissions[4–6] and significantly inflate hospital expenditures. In 1998, ADREs were identified as the sixth leading cause of in-hospital mortality in the United States.[7,8]

In an attempt to reduce drug-related morbidity and mortality, researchers have begun to study clinicians' ability to detect and treat ADREs. Large-scale studies have shown that clinicians taking care of inpatients detect only 5%–15% of drug-related events in hospitals without systematic surveillance systems.[9,10] In contrast, reports from intensive care settings indicate that the presence of a pharmacist on rounds decreases the rate of preventable ADREs by helping intercept errors as well as unrecognized events.[11] These studies have served as the basis for justifying the cost of a pharmacist present on intensive care unit and medical ward rounds in many institutions.

The few published studies that have documented the significance of ADREs in the ED setting[1–3,12] have not

assessed the performance of emergency physicians (EPs) in recognizing such events. This is important because most EDs are not equipped with systematic ADRE surveillance systems and do not have the funding available for a pharmacist to be on call 24 hours a day/7 days a week for the purpose of screening high-risk patients. Given the frequency of ADREs in the ED, it is critical to understand EP performance in detecting ADREs in order to improve quality of care and, if necessary, develop and implement ADRE screening tools to help EPs in this difficult task.

The objectives of this study were to examine EP performance in recognizing ADREs in elder patients who present to our ED and to characterize the events that went unrecognized.

METHODS

Study Design. A prospective observational study was conducted on a convenience sample of elder patients presenting to the ED at Sir Mortimer B. Davis Jewish General Hospital (SMBD-JGH). The study protocol was reviewed and approved by our hospital's institutional review board. Informed written consent was obtained from all subjects.

Study Setting and Population. The SMBD-JGH is a 637-bed adult university teaching hospital in Montreal, Quebec, Canada, with an annual ED census of 60,000 patients. It serves as an urban university teaching hospital as well as a community hospital for the surrounding neighborhood.

Patients older than 65 years of age who were present in the SMBD-JGH ED between January 3, 2003, and April 26, 2003, while the research team was recruiting patients, were eligible for participation. We excluded patients who spoke neither English nor French, were physically unable to sign their name, presented for intentional self-poisonings, were previously enrolled, left against medical advice, or had been seen by a physician involved in the study protocol and ADRE evaluation (CMH and JD). In addition, patients who demonstrated severe cognitive deficits (failed a Short Portable Mental State Questionnaire)[13] and were unable to reflect understanding of this study by answering two questions about the purpose were excluded.

Study Protocol. Patients were recruited Mondays through Fridays between 8 AM and 4 PM. A pharmacy resident (VL or CR) enrolled patients consecutively according to time of ED presentation, starting with those patients who had been in the ED the longest. This allowed us to have the results of diagnostic testing available at the time of ADRE assessment. All data used to determine whether or not the patient experienced an ADRE were collected prospectively.

All EPs were informed of the study by e-mail and flyers before the beginning of the study period. All EPs working at the SMBD-JGH during the study period who were not directly involved in the study protocol or the ADRE evaluations were included.

Once a patient had been enrolled in the study, a pharmacy resident collected data using standardized data collection forms. The pharmacy residents collected data on demographics, ED chief complaint, other patient complaints, medical history, known allergies and medication intolerances, and medication history including supplements, over-the-counter medications, and herbal remedies. Physical examination findings, laboratory test information, diagnostic test results, ED or admission prescriptions, and admission and discharge diagnoses were collected as well. The pharmacy residents reviewed each medication history over the telephone with the patient's community pharmacist(s) for accuracy and completeness. The research team did not intervene in patient care until after the ADRE evaluation and EP interview were completed. The research team did not order any laboratory tests.

Definitions and Identification of ADREs. For study purposes, ADREs were defined as "any unfavorable medical event related to medication use or misuse."[1] This definition comprises adverse drug reactions, adverse drug interactions, drug withdrawal reactions, and adverse events arising from prescription errors and noncompliance.[1] Adverse drug reactions were defined according to the World Health Organization as "noxious and/or unintended responses to medication which occur despite appropriate drug dosage for prophylaxis, diagnosis or therapy of the indicating medical condition."[14] These included abnormal laboratory values incurred because of medication administration. Adverse drug interactions were defined as "noxious and/or unintended effects caused by the coadministration of two or more medications." This included changes in the clinical efficacy of one or more medications caused by the coadministration of another drug. Drug withdrawal reactions were considered whenever a medication that had been taken on a regular basis for at least one week had been abruptly discontinued in the two weeks before the ED visit. The presenting symptoms had to be consistent with a known withdrawal pattern.

We used the reference ranges of our hospital laboratory to define abnormal electrolyte and toxic drug concentrations.

Once all data were collected on a given patient, the pharmacy resident entered the medication list into the MICROMEDEX database.[15] For each medication entered, MICROMEDEX produced an elaborate list of possible ADREs. This list of potential ADREs was searched for any complaints and abnormal laboratory values noted on patient presentation. For any

scenarios that were suspicious for an ADRE but not identified by MICROMEDEX, additional searches were made in MEDLINE through PubMed.[16] As search terms, the generic medication name was used combined with "adverse drug event" or the patient complaint or abnormal laboratory test.

All potential ADREs identified through MICROMEDEX or MEDLINE were further evaluated using the Naranjo APS[17] drug reaction probability scale (Table 1). All potential ADRE cases were discussed by a team consisting of one physician and one pharmacist. This team assigned the Naranjo probability score. Based on prior studies, cases were considered to be ADREs if the final Naranjo score was ≥5. All ADRE cases were reevaluated using the Naranjo scale by a second physician–pharmacist team that was blinded to the assessment of the first team. Agreement between the two evaluating teams was assessed and reported. All differences were resolved through consensus.

At the end of the study period, we reviewed the hospital charts of all patients with ADREs, looking for any alternative diagnoses for the complaints we had ascribed to ADREs that could have been made in follow-up clinics or during admission. No alternative diagnoses were found for any cases ascribed to ADREs. No previously unidentified ADREs could be added at this time.

Abnormal Laboratory Values. Through a carefully designed flagging system, EPs were promptly made aware of any abnormal laboratory values before intervention by the research team. This system was fully functional during the entire study period. As soon as an abnormal laboratory report was received by the ED clerical staff, it was filed in the chart in such a way that the sheet protruded (i.e., flagged). As a result, anyone who picked up the chart was alerted to the presence of an abnormal laboratory value.

Our hospital laboratory has a policy of defining "panic values" for each laboratory test it performs. This system was also in place during the study period. In this scenario, the laboratory technician called the ED unit coordinator (clerical staff) immediately when a panic value had been determined and the ED unit coordinator then brought this to the attention of the EP on duty. The EP was obliged to sign a sheet indicating that he or she had been informed.

Recognition of ADREs by EPs. Once the ADRE assessment was complete for each patient, the pharmacy resident interviewed the treating EP, regardless of whether or not an ADRE had been found. This interview always occurred at the end of the shift. At the beginning of the interview, the pharmacy resident presented a written definition of an ADRE to the EP. The EP was able to request the patient's complete medication list at this time. The EP was then asked whether or not he or she had identified an ADRE. The EPs were subsequently informed of any ADREs the research team found. If an EP was unavailable at the end of a shift, the research team attempted to contact him or her the next day. If the EP who saw the patient originally was neither available at the end of the shift nor scheduled for a shift the next day, the treating EP in charge of the patient's care at the time of the interview was questioned. In only 3% of all scenarios did EPs believe that having access to a complete medication list changed their ADRE assessment.

Some patients evaluated during the daytime had presented to the ED during a previous shift and had been signed over to the EP completing the interview. Because it was possible that an ADRE was forgotten during sign-over, we reviewed all patient charts in which the research team identified an ADRE that had been missed by the EP. We looked for any existing documentation in the chart indicating that an EP had recognized the ADRE on a shift before the interview.

TABLE 1. Naranjo ADRE Probability Scale

	Yes	No	Do Not Know
1. Are there previous *conclusive* reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Modified with permission from Naranjo et al.[17]
Each clinical scenario suspicious for an ADRE was evaluated using this scale. The ADRE probability score was calculated by answering the ten questions for each scenario and adding the points obtained. Scenarios in which less than five points were obtained were considered unlikely to be ADRE related, whereas scores of five or greater were considered ADRE-related scenarios.
ADRE = adverse drug-related event.

Written documentation of the ADRE, withdrawal or omission of the culprit medication on an ED prescription, a reduction in dose, or initiation of a medication to treat an ADRE were considered evidence that the ADRE had been detected.

Classification of ADREs. ADREs were classified as severe if the ADRE mandated patient admission or caused death; moderate if the ADRE required any medical intervention, such as an adjustment in the medication regimen, a radiologic or invasive diagnostic procedure, or any treatment for the ADRE; and mild if no medical intervention was required. Whether an ADRE required medical intervention or not was left to the discretion of the treating EP. ADREs based on abnormal laboratory values were classified in the same manner.

An ADRE was considered to be responsible for the patient's chief complaint whenever the ADRE-related symptoms were the patient's reason for coming to the ED. All other ADREs were considered incidental findings.

An ADRE was considered to have a clinical manifestation whenever the patient reported a symptom related to the ADRE. Clinically silent ADREs were defined as ADREs due to abnormal laboratory values (e.g., a toxic digoxin level in a patient with pneumothorax). Clinically silent ADREs were never classified as chief complaints.

Data Analysis. Data were analyzed using Statview software version 5.0 (SAS Institute, Inc., Cary, NC). Descriptive statistics are expressed as means with standard deviations and 95% confidence intervals (CIs). Determinants of ADRE detection were calculated using odds ratios and also presented with 95% CIs. The performance of EPs in detecting ADREs was calculated by dividing the total number of ADREs recognized by the EPs (as identified by questionnaire and chart review) by the total number of ADREs the research team found. Only ADREs with significant Naranjo scores (≥5) were included in this calculation. The performance of EPs in detection of ADREs was expressed as a percentage with 95% CIs. Agreement between the physician–pharmacist team was assessed using the κ statistic. Sample size was limited by the availability of our pharmacy residents.

RESULTS

Characteristics of Study Subjects. Our study sample consisted of 161 patients. The average age was 78.2 years (95% CI = 76.9 to 79.3), and 50.9% of patients were male and 49.1% female. The average number of comorbid conditions per patient was 4.1 (95% CI = 2.9 to 5.4), while the average number of medications (regular and prn) was 8.4 (95% CI = 7.7 to 9.1). The admission rate in our patient sample was 52.8% (95% CI = 45.1% to 60.4%). A total of 42% of patients presented during the day shift (8 AM to 4 PM), 30% during the evening shift (4 PM to midnight), and 27% during the night shift (midnight to 8 AM). The mean time interval from ED presentation to evaluation by our research team was 18.3 hours (95% CI = 16.4 to 20.2).

Nineteen EPs worked in the SMBD-JGH ED during the study period. All patients seen by a study investigator (JD or CMH) were excluded. From the remaining EPs who treated patients and were interviewed, 12 are board certified in emergency medicine (12 by the Collège des Spécialistes de la Province du Québec, four by the Royal College of Physicians and Surgeons of Canada, and five by the American Board of Emergency Medicine), and five are family physicians with a specialty certificate in emergency medicine. On average, the EPs worked 2.5 shifts (range, 1–3.5) per week in the ED during the study period. The average number of years in practice in emergency medicine was 9.5 (range, 1–21).

Main Results. A total of 37 ADREs were identified in 26 patients. The rate of agreement between the two physician–pharmacist teams on whether or not any given patient had an ADRE was 85% (κ value, 0.6; 95% CI = 0.32 to 0.87). The prevalence of ADREs was 16.2% (95% CI = 10.5% to 22.0%) in our study population. Eleven patients (6.8%; 95% CI = 2.9% to 10.7%) presented to the ED because of an ADRE. All other ADREs (26 of 37) did not represent a chief complaint and were considered to have been found incidentally. Nineteen of 26 patients (11.8% of the total sample; 95% CI = 6.8% to 17.0%) experienced a moderate or severe ADRE.[18]

The EPs identified 51.2% (95% CI = 35.2% to 67.4%) of all ADREs (Figure 1 and Table 2). EPs identified 10 of 11 (91%; 95% CI = 74.1% to 100%) ADREs that constituted the patient's chief complaint versus 34.6% (95% CI = 16.3% to 53%) of ADREs that were found incidentally. EPs identified 13 of 19 (68.4%; 95% CI = 48% to 89%) ADREs that exhibited clinical manifestations and six of 18 (33.3%; 95% CI = 11.3% to 55%) that were clinically silent. The odds ratio for detecting an ADRE with a clinical manifestation as opposed to a silent ADRE was 4.3 (95% CI = 1.1 to 17.2). The treating EPs recognized six of seven (85.7%; 95% CI = 59.8% to 100%) severe, 13 of 23 (56.5%; 95% CI = 36.8% to 77%) moderate, and none of the mild ADREs.

Recognition of ADREs varied with medication class. EPs identified all antibiotic-, hypoglycemic-, and sedative-induced ADREs; only one half of ADREs induced by chemotherapy, nonsteroidal anti-inflammatory drugs, warfarin, and diuretics; and fewer than one half of all other ADREs.

The EPs missed only one severe ADRE in a patient whose ADRE was recognized and treated by the

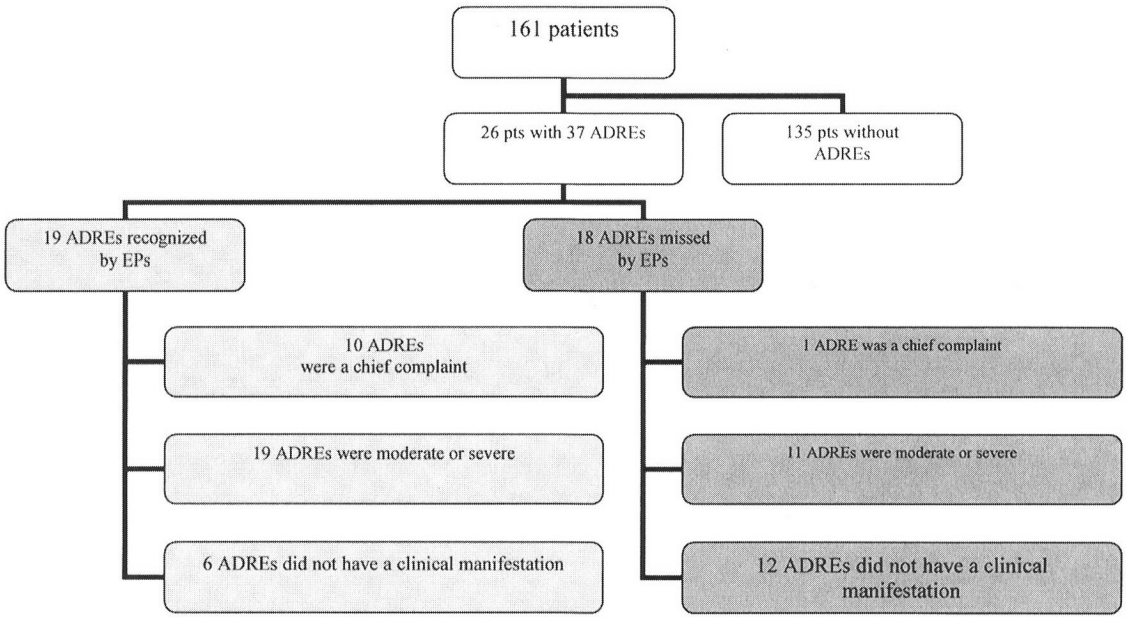

Figure 1. Flow diagram.

admitting team. This was a beta-blocker–induced bradycardia. The patient experienced no untoward event. Eleven of the missed ADREs were abnormal laboratory values in clinically asymptomatic patients. The most dangerous of these was an elevated digoxin level of 3.3 nmol/L in a patient reporting shortness of breath. Two cases of electrolyte abnormalities that were missed may potentially have put the patient at risk if not corrected. The first was a patient who was recently started on desmopressin for urinary incontinence whose serum sodium level had decreased from 142 to 128 mmol/L over two weeks. The desmopressin was discontinued once the EP was notified. The other was a patient on furosemide with a potassium level of 2.9 mmol/L (Table 3).

The EPs identified eight clinical scenarios that they believed were ADREs but for which the research team assigned Naranjo scores of <5 and thus did not meet our threshold to be considered an ADRE. In five of these cases, alternative diagnoses were found that explained the clinical scenarios (Table 4). We did not categorize the remaining three cases as ADREs because we could not exclude alternate diagnoses at the time of the research intervention; the first case was a patient diagnosed with *Clostridium difficile* colitis, the second was a patient with

TABLE 2. ADREs Recognized by the Treating Physicians

Patient No.	ADRE Description	Medication(s)	Contributory Laboratory Values	Preventability	Cc
Severe ADREs					
24	*C. difficile* colitis	Timentin/levofloxacin	*C. difficile* positive	Yes	Yes
50	*C. difficile* colitis	Ciprofloxacin	*C. difficile* positive	No	Yes
55	Neutropenia	Carboplatin/paclitaxel	Absolute neutrophil count 0.5×10^9 cells/L	No	No
71	Gastrointestinal bleeding	Warfarin/acetylsalicylic acid	INR 1.8	Yes	Yes
114	Congestive heart failure	Furosemide withdrawal		Yes	Yes
153	*C. difficile* colitis	Cephalexin	*C. difficile* positive	No	Yes
Moderate ADREs					
31	Bradycardia	Acebutolol		Yes	No
12	Hypoglycemia	Insulin	Glucose 2.8 mmol/L	Yes	No
40	Supratherapeutic INR	Warfarin	INR 9.9	No	No
55	Nausea/vomiting	Carboplatin/paclitaxel		No	No
55	Diarrhea	Carboplatin/paclitaxel		No	Yes
66	Hypokalemia	Indapamide	Potassium 3.1 mmol/L	Yes	No
74	Hypokalemia	Furosemide	Potassium 3.4 mmol/L	Yes	No
95	Hematuria	Warfarin	INR 4.3	Yes	Yes
97	Hypoglycemia	Glyburide/metformin	Glucose 1.7 mmol/L	Yes	Yes
123	Supratherapeutic INR	Warfarin	INR 4.4	Yes	No
150	Hypokalemia	Indapamide	Potassium 3.1 mmol/L	Yes	No
152	Fatigue/weakness	Loxapine/temazepam/trazodone		Yes	Yes
163	Hypoglycemia	Glucophage/glyburide	Glucose 1.0 mmol/L	Yes	Yes

ADRE = adverse drug-related event; INR = international normalized ratio.

TABLE 3. ADREs Missed by the Treating Physicians

Patient No.	ADRE Description	Medication(s)	Contributory Laboratory Values	Preventability	CC
Severe ADREs					
32	Diarrhea	Capecitabine		No	Yes
Moderate ADREs					
12	Epistaxis	Warfarin	INR 4.0	No	No
15	Bradycardia	Metoprolol		Yes	No
15	Supratherapeutic INR	Warfarin	INR 5.5	No	No
15	Hypokalemia	Furosemide	Potassium 3.4 mmol/L	Yes	No
24	Hypokalemia	Furosemide	Potassium 2.9 mmol/L	No	No
70	Hypokalemia	Indapamide	Potassium 3.3 mmol/L	Yes	No
82	Toxic digoxin level	Digoxin	Digoxin level 3.3 mmol/L	Yes	No
82	Gingival bleeding	Warfarin/acetylsalicylic acid	INR 3.7	Yes	No
114	Supratherapeutic INR	Warfarin	INR 3.9	No	No
126	Hyponatremia/nausea	Desmopressin/HCTZ	Sodium 128 mmol/L	Yes	No
Mild ADREs					
2	Ecchymosis and pruritus	Salicylic acid		No	No
32	Hand/foot syndrome	Capecitabine		No	No
40	Thrombocytopenia	Gemcitabine	Platelet count 93 × 10^9/L	No	No
42	Moon facies, swelling	Prednisone		No	No
70	Hyponatremia	Indapamide	Sodium 131 mmol/L	Yes	No
91	Hyponatremia	Amiloride/HCTZ	Sodium 133 mmol/L	Yes	No
104	Hypokalemia	Triamterene/HCTZ	Potassium 3.4 mmol/L	No	No

ADRE = adverse drug-related event; INR = international normalized ratio; HCTZ = hydrochlorothiazide; CC = chief complaint.

colchicine-induced diarrhea, and the third was a case of epistaxis in a patient on salicylic acid. These three patient charts were carefully reviewed at the end of the study period, and no alternative diagnoses were found such that the three ADREs remained plausible. However, according to our protocol, they were not included in the final count of ADREs (Table 4).

The proportion of ADREs recognized was 47.8% (95% CI = 27.4% to 68%) in the first half of the study and 57.1% (95% CI = 31.2% to 83%) in the second half of the study.

DISCUSSION

To the best of our knowledge, this study is the first of its kind to examine the ability of EPs to detect ADREs in the ED setting. The results indicate higher rates of ADRE detection (50.2%) than those reported in the medical literature in other clinical settings

TABLE 4. Clinical Scenarios Suspected to be ADREs by the Treating EPs with Naranjo Scores <5

Patient No.	Suspected ADRE by EP	Medication(s)	Description/Alternate Diagnosis
Alternative diagnosis plausible			
3	Febrile neutropenia	Chemotherapy	Absolute neutrophil count 1.7 × 10^9 cells/L; all cultures negative.
10	CHF, peripheral edema	Metoprolol	Dietary indiscretion and severe tricuspid regurgitation on echocardiography. Maintained on same dose of metoprolol throughout admission with improvement of CHF.
14	Vertigo	Amiodarone	Pontine infarct on MRI/A.
100	Diarrhea	Oxycodone	The EP suspected overflow diarrhea constipation; however, neither rectal examination nor Fleet enema produced stool or resolved the problem.
137	Syncope/hypotension	Enalapril	This patient also had aortic insufficiency and left ventricular ejection fraction of 15%. The enalapril was withheld in the hospital without improvement of the hypotension.
153	Hypotension	Amlodipine/cilazapril	This patient developed antibiotic-induced *C.difficile* colitis and continued to take his regular antihypertensive medications. The primary cause of his low blood pressure was likely dehydration from profuse diarrhea.
No alternate diagnosis found, ADRE plausible			
30	Diarrhea	Ciprofloxacin/amoxicillin	*C. difficile* positive.
142	Diarrhea	Colchicine	This patient had been prescribed colchicine two days PTA and presented with a 24-hour history of diarrhea.
146	Epistaxis	Salicylic acid	Had recurrent epistaxis one week later; the acetylsalicylic acid was discontinued, and the complaint resolved.

ADRE = adverse drug-related event; EP = emergency physician; CHF = congestive heart failure; MRI/A = magnetic resonance imaging / angiography.

(5%–15%).[9,10] There are several plausible explanations to account for this finding. In our study, EPs performed best in detecting ADREs that represented the patients' chief complaints (91%). These made up nearly one third of all ADREs in our study. In these cases, the patients' presenting symptomatology naturally directed the EP's attention to the ADRE. Prompted by the symptom, the EPs were good at linking the complaint to the ADRE. This is in contrast to various inpatient settings in which ADREs often occur as a consequence of treatment of the primary medical condition. In the latter setting, ADREs may less likely be the focus of attention of the treating physicians.[9,10]

The high detection rate of ADREs may have been inflated by the awareness of the EPs of the ongoing study. EPs may have been more attentive to the medication histories and the possibility of ADREs during shifts in which they observed the pharmacy resident enrolling patients. However, it would have been unethical for us not to inform the participating EPs of our study, because their performance was the main objective of our study. In addition, it would have been unethical to withhold information on unrecognized ADREs.

The EPs were more proficient at detecting ADREs with clinical manifestations, even if they were not the patient's chief complaint, compared with silent ADREs. In total, two thirds of clinically silent ADREs were missed. Most of these represented abnormal laboratory values, some of which clearly posed a hazard to the patient. In our small study sample, one patient was found to have an international normalized ratio of 5.5, another had a digoxin level of 3.3 nmol/L, a third had a serum potassium level of 2.9 mmol/L, and a fourth had a serum sodium level of 128 mmol/L that had rapidly declined from 142 mmol/L. All of these patients would have been discharged without adjustment of their medication regimens had the research team not intervened and alerted the EPs. This would have occurred despite an abnormal laboratory value flagging system that has been in place for many years in the ED. Such a system appears to be insufficient to avert missing significant ADREs. This finding is important and should serve as the impetus for the development of systematic ADRE detection tools for the ED. ADRE detection systems should be designed to pinpoint those events that are least likely to be detected by EPs yet present a danger to patients.

The necessary delay in assessing patients for ADREs combined with shift changes introduced the potential for recollection or "sign-over" bias. It was anticipated that newly arriving EPs who were signed over a patient with an ADRE might be less likely to remember an ADRE compared with the first physician who saw the patient. In addition, the first physician who saw the patient would have been more likely to remember the ADRE if interviewed immediately after having seen the patient. This could have led to an underestimation of the performance of EPs. To minimize this bias, all charts of patients with ADREs were reviewed at the end of the study period to search for evidence of ADRE recognition by an EP during a previous shift. Our review was quite exhaustive; it would have missed only ADREs treated by verbal order that was never transcribed or clinically insignificant ADREs requiring no medical treatment. Therefore, we are confident that we did not underestimate the rate of ADRE detection by EPs.

In the present study, we did not address the question of how EPs disclose ADREs to patients. Recent literature indicates that patients desire prompt disclosure of ADREs and counseling on how ADREs can be treated and future events avoided.[19] Time constraints in the ED and lack of knowledge of the circumstances under which the culprit medication was prescribed may make EPs hesitant to disclose ADREs. Given the frequency of ADREs in the ED, we believe it is important that future studies examine the issue of ADRE disclosure in order to assess whether patients' needs are being met.

LIMITATIONS

The main limitation of our study is its sample size. We chose a systematic and exhaustive approach to identify all potential ADREs in order to avoid missing any. This approach required a time-consuming search in two databases (MICROMEDEX and MEDLINE) for each patient we enrolled in the study. The time required to perform the search limited the number of patients we were able to enroll during the study period. Investigators of future studies may choose to use a less extensive process for identification of potential ADREs in the interest of time but will need to consider the potential pitfall of missing ADREs in doing so.

A further limitation arose from the fact that our ethics committee did not grant us permission to use proxy consent for patients with severe cognitive deficits. This limited our ability to detect ADREs that manifested with mental status changes. In addition, we were unable to screen elder patients with advanced dementias who may be at higher risk for noncompliance. This may have led to an underestimation of the rate of ADREs in our study.

For the purposes of our study, we used the World Health Organization definition of ADRE.[14] This definition did not include low prescribed dose as a cause of adverse events. One recent study found that therapeutic drug failure caused by low prescribed dose may be an important cause of preventable adverse events and ED presentation.[20] Future investigators may choose to incorporate low medication dosing in their definition of ADRE.

One of the strengths of our study is our systematic use of a published validated algorithm for confirmation of ADREs.[17] We chose the Naranjo algorithm in particular because it is more user friendly and time efficient than other algorithms while being equally reliable.[21] Both an advantage and a drawback of the Naranjo algorithm is that it considers ADREs as diagnoses of exclusion. The advantage of this is that it avoids overestimation of the rate of ADREs. On the other hand, it makes it highly unlikely to be able to accumulate a high enough point score to consider a scenario an ADRE before all alternative diagnoses have been excluded by laboratory and radiologic testing or by specialist consultation. Practically speaking, this meant that we had to enroll patients who had been in the ED long enough to have access to their diagnostic test results. This is why we enrolled patients who had been in the ED the longest first. This, of course, introduced spectrum bias; patients who stayed longer in the ED longer were likely sicker and more likely to be admitted than patients who stayed in the ED for shorter amounts of time. This is evidenced by the high admission rate in our sample. Healthier patients who required shorter ED stays were less likely to be enrolled in our study. This may have inflated the rate of ADREs observed in our study. However, we doubt that it would have a strong influence on the rate of ADRE detection.

Our study focused on patients older than 65 years of age who presented to the ED. This, of course, limits the applicability of our findings to this high-risk patient population. Our focus was deliberate for two reasons: 1) this patient population has not been studied prospectively in the past, and 2) the high frequency of ADREs in this patient population made it more feasible to study ADRE recognition.

The study was performed at only one center, limiting external validity. Our hospital, however, is reflective of most academic urban EDs throughout North America, and our results are applicable to this setting. The training and level of experience of our group of EPs is reflective of most academic EDs, with the majority of physicians being board certified in emergency medicine and all but two of the remaining family physicians having specialty certificates in emergency medicine.

CONCLUSIONS

Drug-related morbidity and mortality is gaining increasing recognition as an important health hazard. This study adds to a growing body of literature that documents the significance of ADREs in the ED. In our sample of patients, the incidence of ADREs was second only to chest pain as the leading cause of ED presentation. Recognition of ADREs by EPs was good overall, with EPs performing best at detecting ADREs that represented the patients' chief complaints. EPs had the most difficulty in identifying silent ADREs, which nonetheless posed important risks to our patients. Further research is needed to further delineate the impact of ADREs in the ED as well as design detection systems that facilitate the recognition of those ADREs that are most likely to be missed by ED staff.

The authors thank Drs. Alex Guttman, Eddy Lang, and Bernie Unger for their support in bringing this project to completion; Chris Tselios for reviewing the manuscript; all of the emergency physicians, nurses, and unit coordinators at Sir Mortimer B. Davis Jewish General Hospital, without whom this study could not have been conducted; and all of the pharmacy staff, particularly Michael Zelovics, for their support throughout the study.

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